A MOMENTARY LAPSE OF REASON:

META-ANALYTICAL PROGNOSIS OF BRIEF PSYCHOTIC EPISODES

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ACRONYMS, ABBREVIATIONS

BLIPS, Brief Limited Intermittent Psychotic Symptoms

BIPS, Brief Intermittent Psychotic Symptoms

ATPD, Acute and Transient Psychotic Disorder

BPD, Brief Psychotic Disorder

FES, First Episode Schizophrenia

AT A GLANCE

- The prognostic significance of competing operationalizations for brief psychotic episodes is unknown, leading to an untenable source of confusion for patients, carers, clinicians and researchers.
- We presented a meta-analysis of the risk of psychotic recurrence over time in four diagnostic constructs of remitted first episode of brief psychosis, and in a benchmark group of remitted first episode schizophrenia.
- No prognostic difference was found between different operationalizations of brief psychotic episodes at any follow-up timepoint.
- In the longer term, risk of psychotic recurrence was significantly higher in remitted first episode schizophrenia compared with the four groups of brief psychotic episodes.
- Current data should influence the diagnostic practice and clinical services in the management of early psychosis.

ABSTRACT

Importance

The prognostic significance of competing constructs and operationalizations for brief psychotic episodes (Acute and Transient Psychotic Disorder, ATPD; Brief Psychotic Disorder, BPD; Brief Limited Intermittent Psychotic Symptoms, BLIPS; and Brief Intermittent Psychotic Symptoms, BIPS) is unknown.

Objective

To provide a meta-analytical prognosis of the risk of psychotic recurrence in remitted first-episode ATPD, BPD, BIPS, and BLIPS and in a benchmark group of remitted first-episode schizophrenia (FES). We hypothesized a differential risk: FES>ATPD>BPD>BIPS>BLIPS.

Data Sources

Electronic databases were searched until 18th May 2015 along with investigation of citations of previous publications, and a manual search of the reference lists of retrieved articles.

Study Selection

We included original articles that reported the risk of psychotic recurrence at follow-up in remitted patients with first-episode ATPD, BPD, BLIPS, BIPS, and FES.

Data Extraction and Synthesis

Independent extraction by multiple observers. Random effect meta-analysis conducted with the "metaprop","metaninf", "metafunnel", "metabias" packages of STATA 13.1. Moderators were tested with meta-regression analyses, Bonferroni corrected. Heterogeneity was assessed with the I^2 index. Sensitivity analyses tested robustness of results. Publication biases were assessed with funnel plots and Egger's test.

Main Outcome Measure

Proportion of baseline ATPD, BPD, BLIPS, BIPS patients with any psychotic recurrence at 6, 12, 24, and ≥36 months follow-up.

Results

Eighty-two independent studies comprising up to 11133 patients were included. There was no prognostic difference between ATPD, BPD, BLIPS, and BIPS at any follow-up ($p>0.05$). In

the longer term, risk of psychotic recurrence was significantly higher in the FES group (from 78% at 24 months to 84% at ≥36 months) compared with the other four groups (from 39% at 6 months to 51% at ≥30 months). There were no publication biases; sensitivity analyses confirmed robustness of results. Exposure to antipsychotic and gender modulated the meta-analytical estimates (uncorrected threshold).

Conclusions and Relevance

There are no prognostic differences between ATPD, BPD, BLIPS and BIPS. Conversely, there is consistent meta-analytical evidence for a better long-term prognosis of brief acute psychoses compared with remitted schizophrenia. These findings should influence the diagnostic practice and clinical services in the management of early psychosis.

Keywords: Psychosis, Brief, Acute, Schizophrenia, CAARMS, SIPS, ICD, DSM

"The nomenclature of these acute disorders is as uncertain as their nosological status. […] Systematic clinical information that would provide definitive guidance on the classification of acute psychotic disorders is not yet available, and the limited data and clinical tradition that must therefore be used instead do not give rise to concepts that can be clearly defined and separated from each other".

World Health Organization (WHO)[1]

INTRODUCTION

As psychotic disorders of "dramatic symptomatology"[2] but remitting course, brief psychotic episodes represent one of the most intriguing paradoxes in psychiatry. Kahlbaum (1828-1899) first distinguished the typical progressive nature of psychotic forms ("vesania typica") from a separate group of disorders ("dysphrenia") that appeared in an acute and severe form, but then remitted with a full recovery "without leaving a lasting alteration in the elements that serve its expression (1863 page 67)[3]". Kahlbaum's classification did not catch on. Instead, the nosography of Kraepelin (1856–1926) dominated psychiatry and shaped today's diagnostic system.[2] Brief and acute psychoses have been difficult to accommodate as a "third psychosis" in the Kraepelinian dichotomy of dementia praecox and manic-depressive insanity.[4] They have been repeatedly reconceptualised and operationalized without finding a widely agreed nosographic cataloguing either as "bouffée délirante des dégénérés",[5] "cycloid psychoses",[6] "reactive psychoses",[7] "emotional psychoses",[8] "atypical psychoses",[9] or "schizophreniform state"[10] (see Figure 1 for more historical details).

[FIGURE 1]

The nosographic nomadism of brief psychotic episodes continues today. The WHO has brought the above clinical concepts into the ICD diagnostic category of Acute and Transient Psychotic Disorders (ATPD, with six subtypes), a short and remitting episode of psychosis which may last up to three months.[1] Similarly, the American Psychiatric Association has introduced in the DSM the notion of Brief Psychotic Disorder (BPD),

describing the psychosis whose duration is less than a month with full recovery to the premorbid status.[11] Although ATPD and BPD address similar constructs, major operationalization differences exist in terms of their symptomatic features, symptom duration (3 months in ATPD *vs.* 1 month in BPD) and subtypes (schizophreniform-like disorders are included in ATPD) (Table 1). Previous investigations tend to suggest that patients with ATPD and BPD may fare better overall than patients with schizophrenia[12], but the recurrence of subsequent psychotic episodes in ATPD and BPD may be as frequent as in schizophrenia.[13] This literature has not been subject to meta-analysis until now. The current meta-analytical approach is of particular relevance given that operationalization differences may affect their prognostic concordance,[14] and the diagnostic stability of brief psychosis is questionable.[15]

[TABLE 1]

One further complication is that over the past two decades, brief psychotic episodes have been reclassified into pre-psychotic at risk states,[16] as operationalized with the Brief and Limited Intermittent Psychotic Symptoms (BLIPS) concept:[17] “young people with a history of fleeting psychotic experiences that spontaneously resolved within one week”, without the use of antipsychotics.[18] Such a decision was based on the speculation that the BLIPS are the "psychosis equivalent" of transient ischemic attacks (TIAs) observed in neurology: sudden neurological abnormalities resembling a full stroke but settling down within 24 hours, with complete clinical recovery[19] and a limited risk of stroke.[20] A few years later, the duration of Brief Intermittent Psychotic Symptoms (BIPS) was extended from 7 days to 3 months by other authors (Table 1).[21] Although converging studies (Fig 3 in[22]), consensus reviews[16] and a recent meta-analysis[23] have demonstrated the clinical distinctiveness between BLIPS/BIPS and the other two high risk subgroups of attenuated psychosis syndrome and genetic risk and deterioration syndrome,[16] the actual prognostic significance in BLIPS and BIPS, and their validity as the at-risk state as opposed to frank psychosis (as for ATPD/BPD) is unclear.[24] Because of this, the presence of the four competing diagnostic constructs (ATPD, BPD,

BLIPS and BIPS) is a major source of "Babylonian confusion,[25] offering little to guide prognosis or treatment and representing an untenable challenge for patients, carers, clinicians and researchers. Paradoxically, depending on the local availability of high risk services, young adults presenting with brief psychotic episodes features may either receive a diagnosis of established psychosis and antipsychotic treatment (as ATPD/BPD),[26] or an at-risk diagnosis (as BLIPS/BIPS)[27] and undergo the recommended psychological interventions.[28] Prognostic uncertainty is also a major source of heterogeneity undermining research and hindering the discovery of reliable biomarkers to be used in the clinic.[29]

This is the first large-scale meta-analysis primarily testing the differential prognostic significance (predictive validator)[30] of remitted first-episode ATPD, BPD, BLIPS, and BIPS. Second, we choose to compare them with remitted first-episode schizophrenia (FES) to provide a clinical "benchmark". On the basis of spontaneous remission without antipsychotics treatment (in BLIPS/BIPS) and symptoms duration (up to 7 days for BLIPS, less than 4 days/week over 3 months for BIPS, up to 1 continuous month for BPD, and up to 3 continuous months for ATPD), our primary hypothesis was that the risk of a subsequent psychotic recurrence progressively increased across these four competing constructs (BLIPS<BIPS<BPD<ATPD). The secondary hypothesis was that this risk was higher in the benchmark group of remitted FES.

METHODS

Search strategy

Three investigators (MC, GR, CH) conducted two-step literature searches. First, the Web of Knowledge^{SM} database was searched, incorporating both the Web of Science^{SM} and MEDLINE®. The search was extended until 18th May 2015, including abstracts in English language only. The electronic research adopted several combinations of the following keywords: "ATPD", "BPD", "BLIPS", "BIPS", "ICD", "DSM", "psychosis risk", "first episode psychosis", "first episode schizophrenia", "diagnostic stability", "remission" and

"relapse". Second, we used Scopus® to investigate citations of possible previous reviews/meta-analyses on development of another episode of psychosis from an initial first brief psychotic episode, and a manual search of the reference lists of retrieved articles. Articles identified through these two steps were then screened for the selection criteria on basis of abstract reading. The articles surviving this selection were assessed for eligibility on basis of full-text reading, following the MOOSE checklist (eTable1).[31]

Selection criteria

Studies were eligible for inclusion if the following criteria were fulfilled: (a) original articles in English; (b) included a baseline group of patients diagnosed with remitted first-episode brief psychoses, as defined according to standard international classification (ATPD, BPD)[1, 11] or according to the high risk paradigm (BLIPS, BIPS),[32-34] or a comparison benchmark group of remitted FES[1, 11] (see (d)); (c) reported the risk of psychotic recurrence at follow-up. ATPD, BPD, BLIPS and BIPS are per definition brief and remitting. BLIPS/BIPS are antipsychotic naïve or minimally treated, while ATPD/BPD have a favourable response to antipsychotics[35] and they are often (76%[36]) antipsychotic free at follow-up, so that maintenance medication is used less often than schizophrenia.[12] Accordingly, to minimize the potential confounding effect of illness chronicity and prolonged antipsychotic treatments, FES studies were included if they (d) had investigated remitted first-episode patients (as defined in eTable 2b). When data were not directly presented they were indirectly extracted from associated data or corresponding authors were contacted to retrieve additional data. Exclusion criteria were: (a) abstracts, pilot datasets, and paper in languages other than English; (b) articles that were not employing the internationally validated diagnoses for ATPD, BPD, BLIPS, BIPS, and FES; (c) articles with overlapping datasets; (d) high risk samples belonging to the genetic risk and deterioration syndrome and the attenuated psychosis symptoms subgroups; (e) FES studies with samples who had not fully remitted from their first episode; and (f) studies with samples of multi-episode or chronic psychosis. Specifically, in case of multiple publications deriving from the same study population, we

selected the articles reporting the largest and most recent data set. Literature search was summarized according to the PRISMA guidelines.[37]

Recorded variables

Data extraction was independently performed by two investigators (MC, GR). To estimate the primary outcome variable we extracted the baseline sample size and the number of patients with any psychotic disorders at follow-up. To estimate the secondary outcome we additionally collected the number of patients who developed into schizophrenia or affective psychoses at follow-up. We collected additional moderators as indicated in the statistical analysis and performed quality assessment as detailed in eMethods 1.

Statistical analysis

The outcome measure was the risk of psychotic recurrence in patients who have been remitted from their first episode of ATPD, BPD, BLIPS, BIPS (primary outcome), and FES (secondary outcome). This was calculated as the proportion of baseline patients who had any psychotic recurrence at 6, 12, 24 or more than 36 months follow-up. Meta-analysis was conducted with the "metaprop" package[38] of STATA 13.1. This package is specifically developed for pooling proportions in a meta-analysis of multiple studies. The confidence intervals are based on score(Wilson) or exact binomial(Clopper-Pearson) procedures.[39] Metaprop first transforms proportions with the Freeman-Tukey Double Arcsine Transformation[40] to stabilize the variances and then performs a random effect meta-analysis implementing the Der Simonian-Laird method.[41] The influence of moderators was tested using subgroup (type of antipsychotic treatment, study design, remission criteria in FES groups) and meta-regression (publication year, mean age, proportion of females, exposure to antipsychotics from baseline to follow-up, diagnostic criteria used to assess the psychotic episodes at follow-up, quality assessment) analyses. The slope of meta-regression line (β-coefficient: direct (+) or inverse (-)) indicates the strength of a relationship between moderator and outcome. The meta-regressions were Bonferroni corrected for multiple testing.

Heterogeneity among study point estimates was assessed using Q statistics with the proportion of the total variability in the effect size estimates being evaluated with the I^2 index,[42] which does not depend upon the number of studies included. As meta-analysis of observational studies is supposed to be characterized by significant heterogeneity, random effect models were used. Additionally, sensitivity analyses were conducted to investigate the influence of each single study on the overall risk estimate by omitting one study at a time, using STATA's user-written function namely "metainf".[43, 44] A study was considered to be influential if the pooled mean estimate without it was not within the 95% confidence bounds of the overall mean. Publication biases were assessed with the "metafunnel" function of STATA which produced funnel plots for assessing small-study reporting bias in meta-analysis[45] and with the Egger's test[46] in "metabias"[47] function of STATA. Supplementary analyses are detailed in eMethods 2.

RESULTS

Database

Literature search (PRISMA flow-chart eFigure 1) uncovered 82 independent articles, where some contributed with more than one sample. We identified a total of 93 independent samples: 27 ATPD, 22 BPD, 13 BLIPS, 10 BIPS, and 21 FES. Age, gender, diagnostic instrument employed to assign the baseline and the follow-up diagnosis, duration of follow-up and exposure to antipsychotics for each included sample are detailed in eTable 2a and eTable 2b.

Meta-analytical prognosis of brief psychotic episodes

The 93 independent samples reported primary outcome data at different follow-up timepoints (Table 2).

[TABLE 2]

There was significant between-group heterogeneity across all timepoints ($p<0.001$). Across all timepoints, no significant differences were found in the risk of psychotic recurrence between ATPD, BPD, BLIPS and BIPS (Figure 2 & Table 2).

[FIGURE 2]

Comparison with remitted schizophrenia

We found significantly higher risk of psychotic recurrence in the FES group as compared with the other four groups, at and after 24 months. Subgroup analyses in eFigures 2a-c had identified a modulating effect of antipsychotic treatment in the short term (i.e at 6 and 12 months), but no effect for remission criteria and study design.

Meta-regressions, publication biases, and sensitivity analyses

Meta-regressions investigating year of publication, mean age, proportion of females, exposure to antipsychotics from baseline to follow-up, diagnostic criteria used to assess the psychotic episode at follow-up, and quality assessment are appended in eTable 4. At uncorrected threshold for multiple comparisons there was a significant effect for gender (12 and 24 months) and antipsychotic exposure (6, 12, 24 months). Sensitivity analyses were described in eResults 1 and confirmed robustness of the findings. There was no evidence of publication biases as indicated by visual inspections of the funnel plots (eFigure 3a-c) and by the Egger's test for small study effects (at all timepoints $p>0.05$).

Supplementary analyses

No meta-analytical differences in the risk of developing into schizophrenia at 24 months were observed within the ATPD, BPD, BLIPS, and BIPS groups (eFigure 4a and b). No meta-analytical differences in the risk of developing into affective psychoses were detected within the ATPD, BPD, BLIPS, BIPS and FES groups (eFigure 5). The diagnostic stability and

diagnostic change of each category, given psychotic recurrence occurs at follow-up, is detailed in eTable 5.

DISCUSSION

Although brief, the intensity and polymorphism of brief psychotic episodes present a clinical challenge. To address this, we report the first meta-analytical review of prognosis from a large dataset comprised of 82 studies with up to 11133 patients with remitted first-episode ATPD, BPD, BLIPS, and BIPS compared with remitted FES patients. Contrary to our primary hypothesis, there was no prognostic difference between patients with ATPD, BPD, BLIPS, BIPS in all timepoints. In line with our secondary hypothesis, the risk of psychotic recurrence in the long term (at 24 and ≥36 months) was significantly higher in the FES group compared with the other four groups.

This novel study has provided combined robust meta-analytical evidence from 11133 patients with first-episode psychotic disorders, in contrast to single studies, where sample size of brief psychotic episodes is relatively small. Our primary findings of no meta-analytical prognostic differences in the risk of psychotic recurrence between ATPD and BPD are in line with original data indicating a good concordance between the two constructs, further supporting the claim that there is no "clinical, practical, theoretical reason to separate them" (page 15[48]). An earlier study in 42 ATPD patients found that 62% also fulfilled the BPD criteria.[14] A follow-up study in 343 first hospitalized patients showed that 29% were diagnosed with ATPD and 25% with BPD, for an overall kappa score of 0.71.[49] Other studies conducted in 500[50] and 403[51] first-episode patients confirmed similar 2 years[50] and 10 years[51] prospective consistency across ATPD and BPD. Despite this, some notable differences between DSM and ICD are still present. For example, our supplementary analysis restricted to cases who had a psychotic recurrence (eTable 5) showed some between-group differences which were driven by higher risk of recurrent brief psychotic episodes (relapses) in the ATPD

(cycloid psychoses[6]) group, and by the fact that schizophreniform features are coded within the ATPD (subtype acute schizophrenia-like psychotic disorder), while they are coded as an independent schizophreniform disorder in the DSM. These controversies will be addressed by the diagnostic revision planned in the next ICD-11 manual,[15] where only the subtype polymorphic psychotic disorder without symptoms of schizophrenia (F23.0) will be retained as ATPD (see eDiscussion 1).

The absence of a meta-analytical prognostic difference between BLIPS and BIPS calls into question the strict 7 days duration in BLIPS. On one hand, the psychosis threshold is higher in the BIPS than in the BLIPS (psychotic symptoms may last for more than 7 days to 3 months); but, on the other hand, it is lower since the BIPS symptoms should not have urgency features[52] ("urgency is any positive psychotic symptom that is seriously disorganizing or dangerous no matter what the duration", page 15).[53] These two differences may counterbalance each other, and hence explain their comparable risks of psychotic recurrence over time and further suggest a need for some psychometric standardization across the two competing definitions.[54]

Additionally, our meta-analysis suggests that the BLIPS/BIPS are prognostically overlapping with the ATPD/BPD (Table 2), which challenges both the validity of the BLIPS/BIPS as a high risk state for psychosis onset and the arbitrary use[55] of psychosis severity thresholds in this field.[52] The overlap is confirmed by our supplementary analysis showing a similar risk of developing into schizophrenia in BLIPS/BIPS (21%) and in ATPD/BPD (15%) by 24 months (eFigure 4b). The speed of progression to psychotic recurrence is also similar, with a mean time to diagnosis of less than 2 years for both BLIPS/BIPS[56] and ATPD[57]/BPD. Although the authors of the BIPS acknowledged that "patients whose fully psychotic experience is of sufficient short duration to meet DSM criteria for brief psychotic disorder could potentially meet prodromal criteria",[58] this is the first convincing evidence supporting this notion. Our prognostic overlap is further

corroborated by converging evidence indicating that BLIPS/BIPS present distinctive diagnostic,[24] psychopathological,[16] prognostic[59, 60] and therapeutic needs[61] when compared with the other high risk groups (for details see[62]). The level of risk of BLIPS/BIPS is comparable to ATPD/BPD and significantly higher[23, 59] than attenuated psychosis symptoms and genetic risk and deterioration syndrome[16]. Therefore, the mixture of BLIPS/BIPS and attenuated psychotic symptoms is unjustified as a homogeneous group expressing a pre-psychotic risk state. Also, since indicated prevention[63, 64] targets high risk people who do not meet the diagnostic criteria for a disorder[65] (e.g. with attenuated psychosis symptoms), it is problematic that BLIPS/BIPS fall outside this framework, qualifying as prevention of psychotic recurrence[65] (eDiscussion 2).

One possible option would be to drop the BLIPS/BIPS entirely from the clinical high risk rubric. This would mirror the approach of excluding BLIPS/BIPS in the recent DSM-5 Attenuated Psychosis Syndrome.[66] However, adopting only the attenuated psychosis symptoms subgroups may cause a further significant drop in transition risks.[67] Innovative strategies combining homogeneous high risk samples with attenuated psychotic symptoms only and neurodevelopmental deficits may yield a clinically significant risk enrichment (3-years risk of psychosis of 28%).[68] A more complex option would be to accept that the BLIPS/BIPS represents a distinct and separate high risk group[23], which is prognostically overlapping with the ATPD/BPD, in the hope to harmonize the four competing constructs. This would better fit the notion of different levels of risk purported by the clinical staging model.[69] However, it would also require redefining the psychotic threshold to be used in the high risk state accordingly. For instance, compromising on the one-month duration for psychotic symptoms would align the BLIPS/BIPS to that of ATPD in ICD-11 and BPD in DSM-5. Such a cross-diagnostic approach would fit with the DSM-5 which uses the level, the number, and the duration of psychotic signs and symptoms (reality distortion, negative symptoms, disorganization, cognitive impairments, motor symptoms, mood symptoms[70]) to demarcate psychotic disorders from each other,[71] together with the new Clinician-Rated

Dimensions of Psychosis Symptom Severity (C-RDPSS)[72] scale. Given ATPD/BPD are relatively frequent, representing up to 6% of all first-episode psychoses[51] and with an incidence of about 4 per 100 000 population per year,[57] their inclusion in a revised clinical high risk state model may significantly increase the clinical ability to predict later psychotic recurrence. Indeed, early accounts confirmed the diagnostic instability, and change in ATPD/BPD is evident in about half of the patients,[57] stressing that "brief psychotic episodes with an acute onset may be an early manifestation of schizophrenia"[73] and that "should be studied as a potential risk group".[36]

To provide a clinical benchmark, as secondary outcome, we used a comparison group of remitted FES. We showed that brief psychotic episodes have a better long-term outcome than remitted FES after 24 months. The lower relapse risks were remarkable at ≥36 months, when the majority of FES subjects with previous remission had developed another psychotic episode, as compared with only half of those with an initial brief psychotic episode (defined as ATPD, BPD, BLIPS, and BIPS). Supplementary analyses of no significant differences at 6 and 12 months may suggest a possible protective effect of antipsychotic medications on relapse (eFigure 2a), while there were no effects for the type of antipsychotic discontinuation (eFigure 2b) nor the criteria employed to define remission (eFigure 2c). Nevertheless, these findings should be interpreted cautiously, because this study was not primarily designed to test the impact of antipsychotic treatment on relapse prevention (for this see[74-76]). Overall, the reduced risk of psychotic recurrence among brief psychotic episodes is in line with earlier claims (in 1997[73]) and later findings indicating an overall more favourable outcome in the domains of social disability, psychological impairment, and general functioning[77] as compared with schizophrenia spectrum patients. Since our findings are robust and not affected by publication biases, they may serve as reliable predictive validators[30] for the delineation of brief psychotic episodes from remitted schizophrenia (see eDiscussion 3). Data from this study could also be useful for future designation of early intervention programmes. For example, our risk estimates at different timepoints are clinically informative as healthcare

professionals can inform patients and carers about their likely risks at a particular timepoint, since their index episode (see eDiscussion 4).

There are some limitations to this study. Evidence of absence is not absence of evidence.[78] However, our meta-analysis included a large dataset with up to 11133 patients where some statistical significant findings were yielded. Furthermore, we did not investigate outcomes other than psychotic recurrence. There is some evidence that a substantial proportion of ATPD patients may show non psychotic affective episodes during followup.[77] Also, we did not include affective psychoses as additional comparison group. For example, the relationship between brief psychotic episodes and bipolar affective disorders has been questioned.[79] However, pilot literature searches did not uncover enough data for a quantitative meta-analysis of the two points above.

CONCLUSIONS

We found meta-analytical evidence for a better long-term prognosis of brief acute psychoses as compared with remitted schizophrenia, but no prognostic differences between ATPD, BPD, BLIPS and BIPS. Achieving diagnostic consensus across competing diagnostic constructs will greatly assist future attempts to identify the most effective ways to prevent psychotic recurrence after initial brief psychotic episodes.

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REFERENCES

1. World Health Organization. International classification of diseases, tenth revision (ICD-10). *Geneva: WHO, 1990.* 1990.
2. Pillmann F, Marneros A. Brief and acute psychoses: the development of concepts. *Hist Psychiatry.* Jun 2003;14(54 Pt 2):161-177.
3. Kahlbaum L. Die Gruppirung psychischer Krankheiten *(Danzig).* 1863.
4. Kraepelin E. Psychiatrie. Ein Lehrbuch für Studirende und Aerzte. 5., vollständig umgearbeitete Auflage. *(Leipzig: Barth).* 1896.
5. Magnan VaL, M. Les Dégénérés. Etat mental et syndromes épisodiques. *(Paris: Rueff).* 1895.
6. Leonhard K. Die Aufteilung der endogenen Psychosen. 1. Auflage *(Berlin: Akademie-Verlag).* 1957.
7. Jaspers K. *General Psychopathology*. Chicago: University of Chicago Press; 1963.
8. Störring GE, Suchenwirth R, Völkel H. Emotionalität und cycloide Psychosen. *Psychiatrie, Neurologie und Medizinische Psychologie.* 1962;14:85-97.
9. Mitsuda H. The concept of "atypical psychoses" from the aspect of clinical genetics. *Acta Psychiatr Scand.* 1965;41(3):372-377.
10. Langfeldt G. The schizophreniform states. *Copenhagen: E. Munksgaard.* 1939.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. *Washington, DC: American Psychiatric Association.* 2013.
12. Pillmann F, Marneros A. Longitudinal follow-up in acute and transient psychotic disorders and schizophrenia. *Br J Psychiatry.* Sep 2005;187:286-287.
13. Pillmann F, Haring A, Balzuweit S, Marneros A. A comparison of DSM-IV brief psychotic disorder with "positive" schizophrenia and healthy controls. *Compr Psychiatry.* Sep-Oct 2002;43(5):385-392.
14. Pillmann F, Haring A, Balzuweit S, Bloink R, Marneros A. The concordance of ICD-10 acute and transient psychosis and DSM-IV brief psychotic disorder. *Psychol Med.* Apr 2002;32(3):525-533.
15. Castagnini A, Foldager L. Epidemiology, course and outcome of acute polymorphic psychotic disorder: implications for ICD-11. *Psychopathology.* 2014;47(3):202-206.
16. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The Psychosis High-Risk State A Comprehensive State-of-the-Art Review. *Jama Psychiatry.* Jan 2013;70(1):107-120.
17. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Australian & New Zealand Journal of Psychiatry.* 2005;39(11-12):964-971.
18. Yung AR, McGorry PD, McFarlane CA, et al. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull.* 1996;22(2):283-303.
19. Kistler JP, Ropper AA, Martin JB. Cerebrovascular diseases. In: Wilson JD, Braunwald E, Isselbacher KJ, et al., eds. *Harrison's Principles of Internal Medicine*. New York, NY: McGraw-Hill; 1991:1977-2002.
20. Wolf ME, Held VE, Hennerici MG. Risk scores for transient ischemic attack. *Front Neurol Neurosci.* 2014;33:41-68.
21. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin.* 2003;29(4):703-715.
22. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr Bull.* Jan 2014;40(1):120-131.

23. Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. *Eur Psychiatry.* Mar 2015;30(3):388-404.

24. Winton-Brown TT, Harvey SB, McGuire PK. The diagnostic significance of BLIPS (Brief Limited Intermittent Psychotic Symptoms) in psychosis. *Schizophr Res.* Sep 2011;131(1-3):256-257.

25. Schultze-Lutter F, Schimmelmann BG, Ruhrmann S. The near Babylonian speech confusion in early detection of psychosis. *Schizophr Bull.* Jul 2011;37(4):653-655.

26. Zhang JP, Gallego JA, Robinson DG, et al. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol.* Jul 2013;16(6):1205-1218.

27. Fusar-Poli P, Yung AR, McGorry P, van Os J. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychol Med.* Jan 2014;44(1):17-24.

28. Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. *Bmj.* 2013;346:f185.

29. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry.* Dec 2012;17(12):1174-1179.

30. Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry.* Jan 2003;160(1):4-12.

31. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama.* Apr 19 2000;283(15):2008-2012.

32. Yung AR, Phillips LJ, Yuen HP, McGorry PD. *Comprehensive Assessment of at Risk Mental State.* Parkville Victoria, The PACE Clinic, ORYGEN Research Centre, University of Melbourne, Department of Psychiatry; 2006.

33. McGlashan TH, Walsh B, Wood SJ. *The Psychosis-Risk Syndrome. Handbook for Diagnosis and Follow-up.* New York: Oxford University Press; 2010.

34. Riecher-Rossler A, Aston J, Ventura J, et al. The Basel screening instrument for psychosis (BSIP): Development, structure, reliability and validity. *Fortschritte Der Neurologie Psychiatrie.* Apr 2008;76(4):207-216.

35. Castagnini A, Berrios GE. Acute and transient psychotic disorders (ICD-10 F23): a review from a European perspective. *Eur Arch Psychiatry Clin Neurosci.* Dec 2009;259(8):433-443.

36. Correll CU, Smith CW, Auther AM, et al. Predictors of remission, schizophrenia, and bipolar disorder in adolescents with brief psychotic disorder or psychotic disorder not otherwise specified considered at very high risk for schizophrenia. *J Child Adolesc Psychopharmacol.* Oct 2008;18(5):475-490.

37. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.

38. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health.* 2014;72(1):39.

39. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med.* Apr 30 1998;17(8):857-872.

40. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Annals of Mathematical Statistics.* 1950;21:607-611.

41. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* Sep 1986;7(3):177-188.

42. Lipsey M, Wilson D. *Practical Meta-analysis*. Thousand Oaks, CA: Sage Publications; 2000.

43. Steichen T. Nonparametric trim and fill analysis of publication bias in meta-analysis. . *Stata Technical Bulletin, StataCorp LP.* 2001:10-57.

44. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol.* Oct 2008;61(10):991-996.

45. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ.* Jul 14 2001;323(7304):101-105.

46. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* Sep 13 1997;315(7109):629-634.

47. Harbord R, Harris R, Sterne A. Updated tests for small-study effects in meta-analyses. 2009;9(2):197-210.

48. Marneros A, Pillmann P. *Acute and transient psychoses*. Cambridge: Cambridge University Press; 2004.

49. Moller HJ, Jager M, Riedel M, et al. The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: assessing courses, types and time stability of diagnostic classification. *Eur Psychiatry.* May 2011;26(4):231-243.

50. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard International First-Episode Project: two-year stability of ICD-10 diagnoses in 500 first-episode psychotic disorder patients. *J Clin Psychiatry.* Feb 2011;72(2):183-193.

51. Heslin M, Lomas B, Lappin JM, et al. Diagnostic change 10 years after a first episode of psychosis. *Psychol Med.* May 4 2015:1-13.

52. Fusar-Poli P, Van Os J. Lost in transition: setting psychosis trehsold in prodromal research. *Acta Psychiatr Scand.* 2013:in press.

53. McGlashan T, Walsh B, Woods S. *The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-Up*: Oxford Univ. Press; 2010.

54. Fusar-Poli P, Cappucciati M, Rutigliano G, et al. At risk or not at risk? Meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. 2015:in press.

55. Yung AR, Nelson B, Thompson A, Wood SJ. The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? *Schizophr Res.* Jul 2010;120(1-3):1-6.

56. Kempton M, Bonoldi I, Valmaggia L, McGuire P, Fusar-Poli P. Speed of psychosis progression in people at ultra high clinical risk: a complementary meta-analysis. *JAMA Psychiatry.* 2015.

57. Queirazza F, Semple DM, Lawrie SM. Transition to schizophrenia in acute and transient psychotic disorders. *Br J Psychiatry.* 2014;204:299-305.

58. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull.* 2003;29(4):703-715.

59. Nelson B, Yuen K, Yung AR. Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? *Schizophr Res.* Jan 2011;125(1):62-68.

60. Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK. Outreach and support in south London (OASIS), 2001-2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. *Eur Psychiatry.* Jun 2013;28(5):315-326.

61. Fusar-Poli P, Frascarelli M, Valmaggia L, et al. Antidepressant, antipsychotic and psychological interventions in subjects at high clinical risk for psychosis: OASIS 6-year naturalistic study. *Psychol Med.* Apr 2015;45(6):1327-1339.

62. Fusar-Poli P, Cappucciati M, Borgwardt S, et al. Heterogeneity of risk for psychosis within subjects at clinical high risk: meta-analytical stratification *JAMA Psychiatry.* 2016:in press.

63. Mrazek P, Haggerty R. *Reducing risks for mental disorders: Frontiers for preventive intervention research*. Washington: National Academy Press; 1994.

64. Gordon RS, Jr. An operational classification of disease prevention. *Public Health Rep.* Mar-Apr 1983;98(2):107-109.

65. WHO. *Prevention of Mental Disorders. Effective Interventions and Policy Options.* Geneva: Department of Mental Health and Substance Abuse; 2004.

66. Fusar Poli P, Carpenter W, Wood S, McGlashan T. Attenuated Psychosis Syndrome: ready for DSM-5.1 ? *Annual Review of Clinical Psychology.* 2014;10(April 2014):in press.

67. Simon AE, Umbricht D, Lang UE, Borgwardt S. Declining transition rates to psychosis: The role of diagnostic spectra and symptom overlaps in individuals with attenuated psychosis syndrome. *Schizophr Res.* Nov 2014;159(2-3):292-298.

68. Cornblatt BA, Carrion RE, Auther A, et al. Psychosis Prevention: A Modified Clinical High Risk Perspective From the Recognition and Prevention (RAP) Program. *Am J Psychiatry.* Jun 5 2015:appiajp201513121686.

69. McGorry PD. Early clinical phenotypes, clinical staging, and strategic biomarker research: building blocks for personalized psychiatry. *Biol Psychiatry.* Sep 15 2013;74(6):394-395.

70. Mattila T, Koeter M, Wohlfarth T, et al. Impact of DSM-5 Changes on the Diagnosis and Acute Treatment of Schizophrenia. *Schizophr Bull.* Dec 20 2014.

71. Heckers S, Barch DM, Bustillo J, et al. Structure of the psychotic disorders classification in DSM-5. *Schizophr Res.* Oct 2013;150(1):11-14.

72. Tandon R, Gaebel W, Barch DM, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res.* Oct 2013;150(1):3-10.

73. Jorgensen P, Bennedsen B, Christensen J, Hyllested A. Acute and transient psychotic disorder: a 1-year follow-up study. *Acta Psychiatr Scand.* Aug 1997;96(2):150-154.

74. Kishimoto T, Agarwal V, Kishi T, et al. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. *Mol Psychiatry.* Jan 2013;18(1):53-66.

75. Leucht S, Barnes TR, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry.* Jul 2003;160(7):1209-1222.

76. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet.* Jun 2 2012;379(9831):2063-2071.

77. Marneros A, Pillmann F, Haring A, Balzuweit S, Bloink R. What is schizophrenic in acute and transient psychotic disorder? *Schizophr Bull.* 2003;29(2):311-323.

78. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ.* Aug 19 1995;311(7003):485.

79. Marneros A, Pillmann F, Haring A, Balzuweit S, Bloink R. The relation of "acute and transient psychotic disorder" (ICD-10 F23) to bipolar schizoaffective disorder. *J Psychiatr Res.* May-Jun 2002;36(3):165-171.

Figure 1. Historical Genealogy of Current Competing Diagnostic Constructs for Brief Psychotic Episodes, Adapted from[48]

Table 1. Competing Current Diagnostic Operationalizations for Brief Psychotic Episodes

	CLINICAL HIGH RISK CLASSIFICATION FOR BRIEF PSYCHOTIC EPISODES		**STANDARD CLASSIFICATION FOR BRIEF PSYCHOTIC EPISODES**	
	Brief Intermittent Psychotic Symptom Prodromal Syndrome SIPS *Version 5.0*[33]	**Brief Limited Intermittent Psychotic Symptoms Group CAARMS *Version 12/2006*[32]**	**Acute and Transient Psychotic Disorder ICD-10 Classification of Mental and Behavioural Disorders[1]**	**Brief Psychotic Disorder DSM-5 Diagnostic and Statistical Manual of Mental Disorders[11]**
Symptoms	At least one of the SOPS P1-P5 Scales is scored 6	At least one of the CAARMS P1-P2-P4 Severity Scales is scored 6 or P3 is scored ≥ 5	Delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these	At least one of the following symptoms. At least one of these must be (1), (2), or (3): 1. Delusions 2. Hallucinations 3. Disorganized speech (e.g., frequent derailment or incoherence) 4. Grossly disorganized or catatonic behaviour
Onset	Symptoms should have reached a psychotic level of intensity in the previous 3 mo	Symptoms should have been present in the previous 12 mo and for not longer than 5 y	Symptoms should have an acute onset, i.e. the time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed 2 wk	Symptoms should have a sudden onset, i.e. a change from a non-psychotic state to a clearly psychotic state within 2 wk, usually without a prodrome
Duration and frequency	Up to 3 mo, at a frequency of at least several min per d at least once per mo but less than one h per d for 4 d per wk in the past mo	Up to 7 d, at a frequency of at least 3–4 times a wk when lasting at least 1 h or at least a daily presence when lasting less than 1 h	*F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia:* Up to 3 mo, for at least several h *F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia:* Up to 1 mo, for the majority of time *F23.2 Acute schizophrenia-like psychotic disorder*: Up to 1 mo, for the majority of time *F23.3 Other acute predominantly delusional psychotic disorder:* Up to 3 mo, for the majority of time	At least 1 d, up to 1 mo

Level of functioning	No social/occupational dysfunction requirement	30% drop in SOFAS score from premorbid level, sustained for a mo, within past 12 mo or SOFAS score<50 for past 12 mo or more	No social/occupational dysfunction requirement	No social/occupational dysfunction requirement
Exclusion criteria	Symptoms are seriously disorganizing and dangerous	-	-	-
	Symptoms are strongly intertwined temporally with substance use episodes (substance-induced psychosis may be considered)	Symptoms occur only during peak intoxication from a substance known to be associated with psychotic experiences (e.g. hallucinogens, amphetamines, cocaine)	Evidence of recent psychoactive substance use sufficient to fulfil the criteria of intoxication (F1x.0), harmful use, (F1x.1), dependence (F1x.2) or withdrawal states (F1x.3 and F1x.4). Presence of organic brain disease (F0) or serious metabolic disturbances affecting the central nervous system (this does not include childbirth). Perplexity, misidentification, or impairment of attention and concentration fulfil the criteria for *Delirium, not induced by alcohol and other psychoactive substances* (F05-A)	Symptoms are due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or to a general medical condition
	Symptoms are better accounted for by another DSM diagnosis	-	Symptoms meet diagnostic criteria for manic episode (F30), depressive episode (F32), or recurrent depressive disorder (F33)	Symptoms are better explained by major depressive or bipolar disorder with psychotic features
	Past psychosis ruled in according to information obtained through the initial screen and evaluated using the POPS	The person has had a previous psychotic episode (treated or untreated)		Symptoms are better explained by another psychotic disorder such as schizophrenia or catatonia
	-	Symptoms do not resolve spontaneously* (*without antipsychotic medication)	-	-

CAARMS, Comprehensive Assessment of At Risk Mental State; d, day; GAF, Global Assessment of Functioning; h, hour; ICD-10, The International Classification of Diseases; DSM (-V), Diagnostic and Statistical Manual of Mental Disorders; min, minute; mo, month; POPS, Presence of Psychotic Symptoms criteria; SIPS, Structured Interview for Prodromal Syndromes; SOFAS, Social and Occupational Functioning Assessment Scale; wk, week.

Figure 2. Meta-analytical Prognosis of Brief Psychotic Episodes over Follow-up Time. * $p<0.05$, ** $p<0.001$.

Table 2 to Figure 2

	Follow-up											
	6 months			12 months			24 months			≥36 months		
Samples (n)	25			46			35			42		
Subjects (n)	1311			1833			1669			11133		
BLIPS (mean,95%CI)	0.08	0.00	0.23	0.28	0.08	0.52	0.32	0.11	0.57	0.30	0.12	0.52
BIPS (mean, 95%CI)	0.22	0.09	0.36	0.35	0.23	0.48	0.43	0.26	0.61	0.46	0.32	0.61
ATPD (mean, 95%CI)	0.13	0.09	0.18	0.30	0.19	0.42	0.38	0.27	0.48	0.54	0.41	0.66
BPD (mean, 95%CI)	0.20	0.08	0.36	0.31	0.12	0.52	0.46	0.31	0.60	0.53	0.34	0.72
FES (mean, 95%CI)	0.30	0.15	0.48	0.42	0.30	0.54	0.78	0.58	0.93	0.84	0.70	0.94
BLIPS vs BIPS vs ATPD vs BPD Test for between group heterogeneity (Q, p)	4.71	0.19		0.90	0.83		1.20	0.75		3.65	0.30	
BLIPS vs BIPS vs ATPD vs BPD vs FES Test for between group heterogeneity (Q, p)	7.63	0.11		2.36	0.67		11.97	0.02		16.97	<0.001	

BLIPS, Brief and Limited Intermittent Psychotic Symptoms; BIPS, Brief Intermittent Psychotic Symptoms; ATPD, Acute and Transient Psychotic Episode; BPD, Brief Psychotic Disorder; Overall risk of psychotic recurrence across BLIPS, BIPS, ATPD, BPD combined together: 6 months 0.12 (95% CI 0.07-0.17), 12 months 0.30 (95% CI 0.22-0.39), 24 months 0.39 (95% CI 0.32-0.47), 36 months 0.51 (95% CI 0.41-0.61); BLPS n=168, BIPS n=125, BPD n=308, ATPD n=10645, FES n=1201. The index episode is defined at the remission of the first episode of BLIPS, BIPS, ATPD, BPD, and FES. Details on the definition of the index episode are appended in eDiscussion 4.